Selinexor Positive Benefit-Risk for Triple-class Refractory Multiple Myeloma (MM)

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Karyopharm Therapeutics

Oncologic Drugs Advisory Committee

Selinexor Accelerated Approval NDA for Triple-class Refractory Multiple Myeloma (MM)

Tanya Lewis

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Selinexor Agenda

Unmet Need in Triple-class Refractory MM	**Paul Richardson, MD** Clinical Program Leader and Director of Clinical Research Jerome Lipper Multiple Myeloma Center Dana Farber Cancer Institute, Boston, Massachusetts
Efficacy	**Jatin Shah, MD** Senior Vice President, Clinical Development Karyopharm Therapeutics
Safety	**Michael Kauffman, MD, PhD** CEO and Chief Medical Officer Karyopharm Therapeutics
Clinical Perspective	**Sundar Jagannath, MD** Director of the Multiple Myeloma Program and Professor of Medicine The Tisch Cancer Institute, Mount Sinai, New York
Conclusion	**Sharon Shacham, PhD** President and Chief Scientific Officer Karyopharm Therapeutics

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Selinexor is an Oral, Novel Agent Offering New Pathway to Treat Triple-class Refractory MM

- Selective inhibitor of exportin 1 (XPO1)

Proposed Indication for Accelerated Approval in Triple-class Refractory Multiple Myeloma

- Selinexor, an oral XPO1 inhibitor, is indicated in combination with dexamethasone for the treatment of patients with relapsed refractory multiple myeloma (RRMM) who have received at least 3 prior therapies and whose disease is refractory to
  - at least 1 proteasome inhibitor (PI)
  - at least 1 immunomodulatory agent (IMiD)
  - an anti-CD38 monoclonal antibody (mAb)

Patients with Triple-class Refractory MM Have Exhausted All Effective Treatment Options

- Myeloma refractory to the 3 most effective classes of anti-myeloma therapies
- Myeloma refractory to glucocorticoids, including dexamethasone
- Median survival of 3.5 to 5.6 months

STORM Part 2 Met Prespecified Primary Endpoint of Overall Response Rate

- Results demonstrate selinexor efficacy in patients with triple-class refractory multiple myeloma
  - ORR and depth of response comparable to prior anti-MM accelerated approvals for less refractory disease

Selinexor has Well-characterized Safety Profile

- Common AEs
  - Thrombocytopenia, nausea / vomiting, fatigue, decreased appetite
- Physicians able to prevent, monitor, and manage AEs
  - Educational programs and materials for physicians and patients

Selinexor Fulfills Criteria for Accelerated Approval in Patients with Triple-class Refractory MM

Accelerated Approval Criteria	Fulfillment
Serious condition	✓ Short median OS in triple-class refractory MM
Meaningful advantage over available therapy	✓ No effective therapies ✓ ORR of 25.4% in triple-class refractory MM
Demonstrates effect on endpoint that is reasonably likely to predict clinical benefit	✓ ORR predicts for longer OS in patients with advanced MM ✓ ORR in triple-class refractory MM similar to accelerated approvals in single- or double-class refractory MM

Recent Accelerated Approvals in Multiple Myeloma Based on Phase 2 Studies

Therapy	Refractory Class	ORR	sCR / VGPR	Approval
Carfilzomib[1]	Single	22.9%	5.3%	Each granted regular approval based on successful confirmatory study
Pomalidomide[2] + low-dose dexamethasone	Single and Double	29.2%	0.9%	
Daratumumab[3]	Double	29.2%	12.3%	

- Study design, number of patients and endpoints similar to STORM study
  - None studied in triple-class refractory disease

1. Kyprolis USPI (2018); 2. Pomalyst USPI (2018); 3. Darzalex USPI (2018)
VGPR = Very Good Partial Response; sCR = Stringent Complete Response

BOSTON Phase 3 Study

BOSTON Phase 3 RCT Fully Enrolled, but Approval Would Not Occur for At Least 2 Years

- Potential approval in second half 2021
  - NDA submission Q4, 2020
- Designed to confirm clinical benefit of selinexor
  - Selinexor + bortezomib + low-dose dexamethasone ***vs*** bortezomib + low-dose dexamethasone
- BOSTON design agreed upon with FDA
- Patients with triple-class refractory myeloma need urgent access to selinexor

Unmet Need in Multiple Myeloma

Paul Richardson, MD

Clinical Program Leader and Director of Clinical Research

RJ Corman Professor of Medicine, Harvard Medical School

Jerome Lipper Multiple Myeloma Center

Dana Farber Cancer Institute

Boston, Massachusetts

Multiple Myeloma is Second Most Common Hematological Cancer and Incurable

- > 12,900 patients will die in US in 2019[1]
- 7-fold higher risk of infection[2]
  - Infectious complications a major cause of death
  - Profound immune suppression characteristics in advanced disease
  - Multisystem organ dysfunction, including renal failure, typical
- Mortality rate increases with each relapse as myeloma becomes more refractory to treatment[3]
  - Highly complex mechanisms of resistance[4]

1. American Cancer Society, 2019; 2. Blimark, 2015; 3. Kumar, 2017; 4. Laubach, 2016

Three Classes of Approved Anti-myeloma Therapies with Single-Agent Efficacy

Class	Single Agent (with or without steroids)	Combination Therapy
Immunomodulatory agents (IMiD)	**Lenalidomide, Pomalidomide**	Thalidomide (and dexamethasone alone)
Proteasome inhibitors (PI)	**Bortezomib, Carfilzomib**	Ixazomib (with lenalidomide)
Anti-CD38 mAb	**Daratumumab**	--
Glucocorticoid	Dexamethasone, Prednisone	Various combinations
Alkylating agents	Carmustine, Melphalan, Cyclophosphamide	Various combinations
Anthracyclines	--	Doxorubicin and Bortezomib
Anti-SLAM7 (CS1) mAb	--	Elotuzumab and Lenalidomide or Pomalidomide
HDAC inhibitors	--	Panobinostat and Bortezomib

Dexamethasone Not Effective in Triple-class Refractory Multiple Myeloma

- Low-dose dexamethasone (160 mg / 28 days)
  - Experts in relapsed refractory MM developed a consensus statement that low-dose shows no single agent activity in these patients[1]
- High-dose dexamethasone (480 mg / 28 days) has minimal activity

Studies with High-dose Dexamethasone	Response Rates	Single-agent Efficacy Therapies Patients Did NOT Recieve
Alexanian 1986	27%	Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, Daratumumab
Richardson 2005	18%	
San Miguel 2013[2]	4%	Pomalidomide, Carfilzomib, Daratumumab

1. Dexamethasone white paper
2. Pomalidomide USPI, 2018

Patients with Triple-class Refractory MM Have Exhausted Effective Treatment Options

- Refractory disease is defined as no response or progression while on, or within 60 days following, therapy[1]

Class	Definition of Class Refractory
Single-class Refractory	Refractory to either PI or IMiD
Double-class Refractory	Refractory to both PI and IMiD
Triple-class Refractory	Refractory to PI, IMiD, and CD-38 mAb Most received all 5 major drugs[2]

1. Richardson, 2003; 2. Lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab
IMiD=immumodulatory imide drug; mAb=monoclonal antibody; PI=proteasome inhibitor

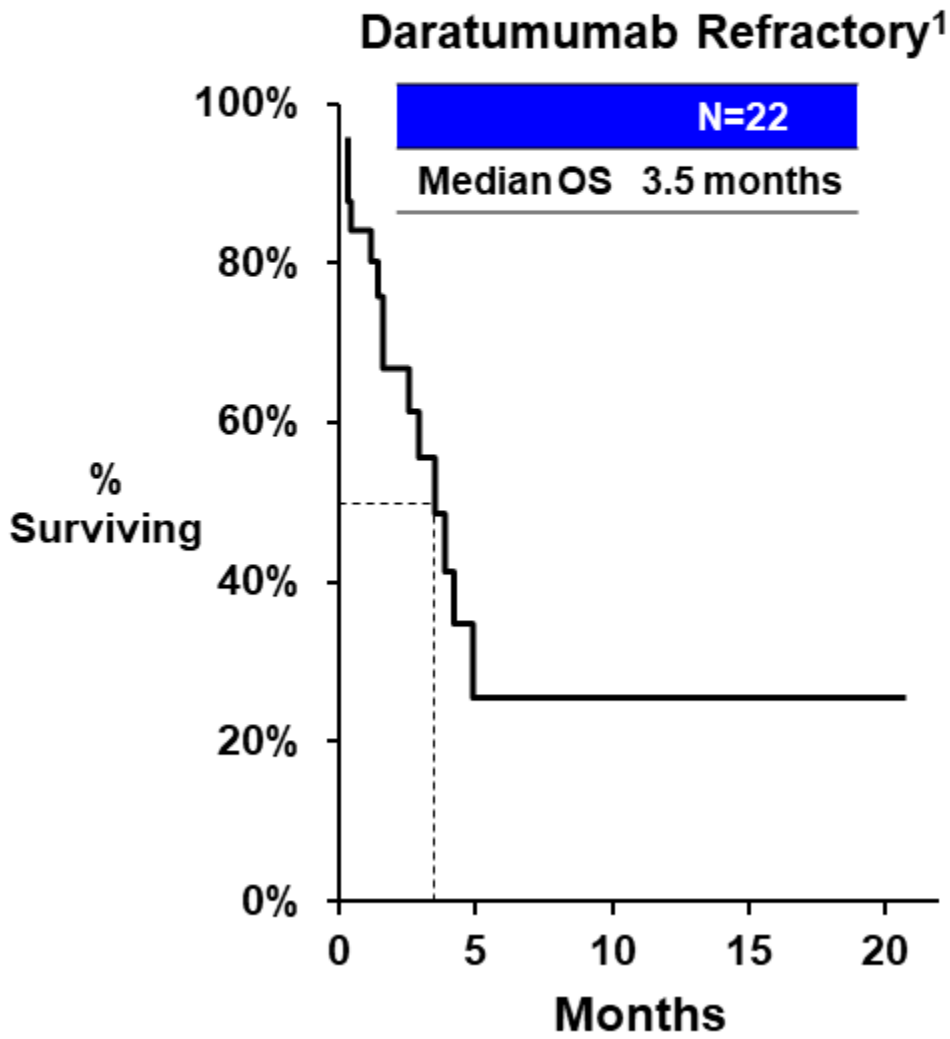
Response Rates in MM Correlate with Clinical Benefit and Improved Patient Outcome

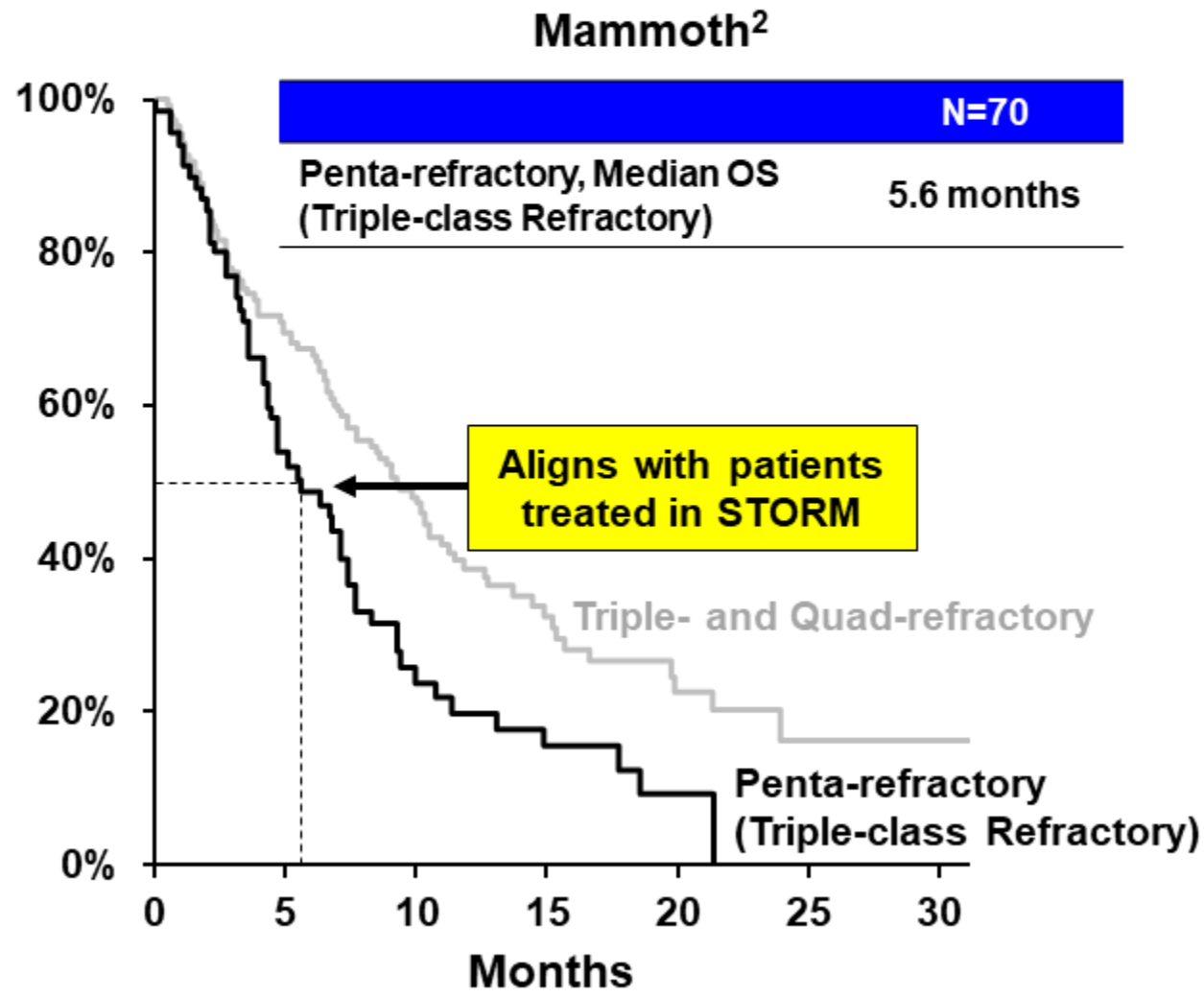
- IMWG established accepted and uniform MM-specific response criteria to facilitate precise evaluation of efficacy[1]
- Response results in reversed or minimized end-organ damage
- Response correlates with improved survival in myeloma
- ≥ minimal response matters in relapsed and refractory MM[2]

- In relapsed refractory AML, there is inconsistent correlation between responses and overall survival[3,4]

1. Rajkumar, 2015; 2. Richardson, 2005; 3. Stone, 2017; 4. Ravandi, 2015
IMWG: International Myeloma Working Group

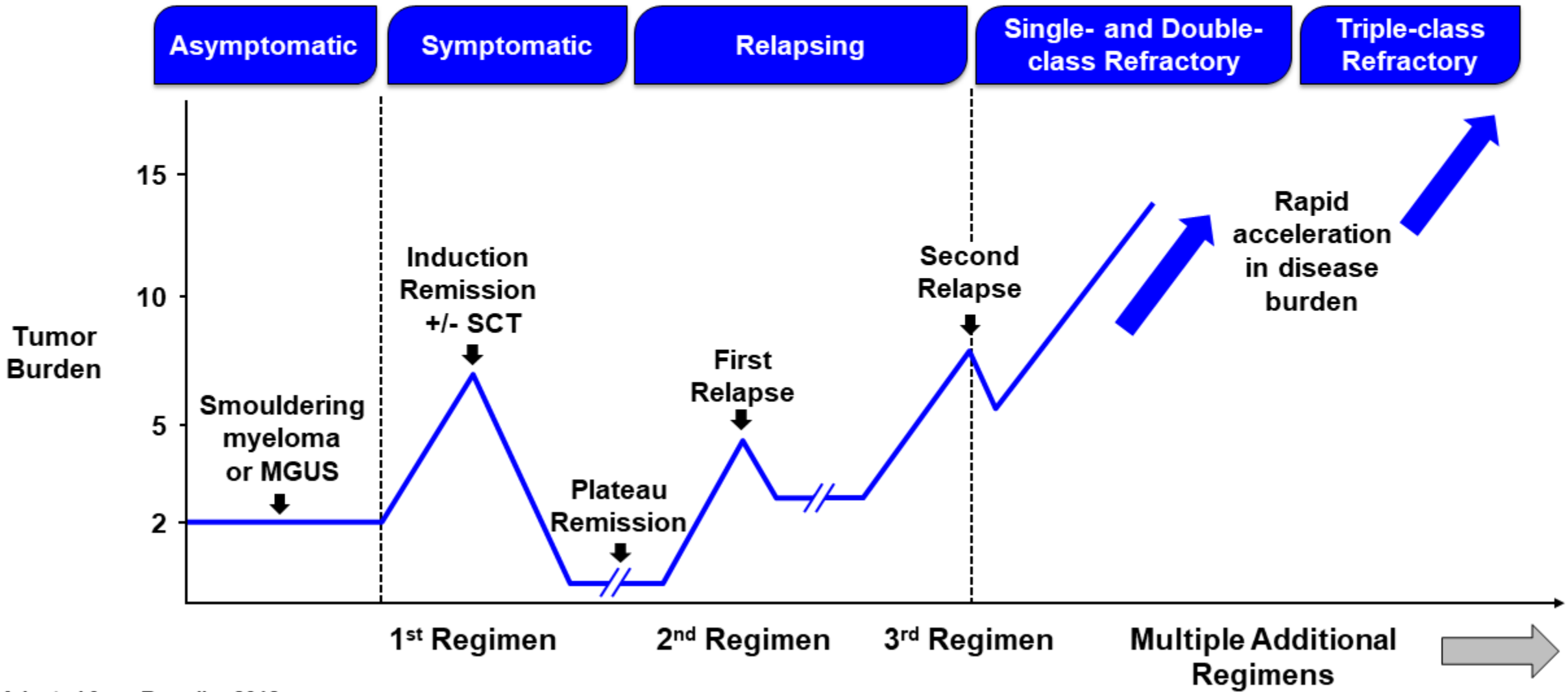
Survival for Heavily Pretreated Patients with Relapsed and Refractory MM is Short





1. Pick, 2018; 2. Gandhi, ASH 2018

Myeloma Rapidly Accelerates Following Relapse and Development of Refractory Disease



1. Adapted from Borrello, 2012

Serious Adverse Events are Common in Patients with Heavily Pretreated Refractory Myeloma

Small Molecule-based Therapies	Pomalidomide[1] (N=107)	Pomalidomide + Low-dose Dex[1] (N=112)	Carfilzomib[2] (N=266)	Carfilzomib[3] (N=157)
Prior treatment regimens, median	5	5	5	5
PI and IMiD refractory	59%	62%	80%*	62%
SAEs	67%	62%	47%	59%
AEs leading to death	7%	5%	4%	10%

* Refractory or intolerant to Bortezomib and Lenalidomide

1. FDA SBA, 2013; 2. Siegel, 2012; Onyx ODAC Briefing Book, 2012; 3. Hajek, 2017 (not submitted for FDA approval), Dex = Dexamethasone

Urgent Need for New, Novel Therapies for Patients with Triple-class Refractory MM

- No approved treatments with demonstrated benefit for patients with triple-class refractory MM[1,2]
- Primary goal: rapidly control disease and reduce tumor burden
- Critical to evaluate new agents in real-world patients
  - Multiple comorbidities, concomitant medications
- Selinexor: a key new treatment option to provide clinical benefit to patients with triple-class refractory multiple myeloma

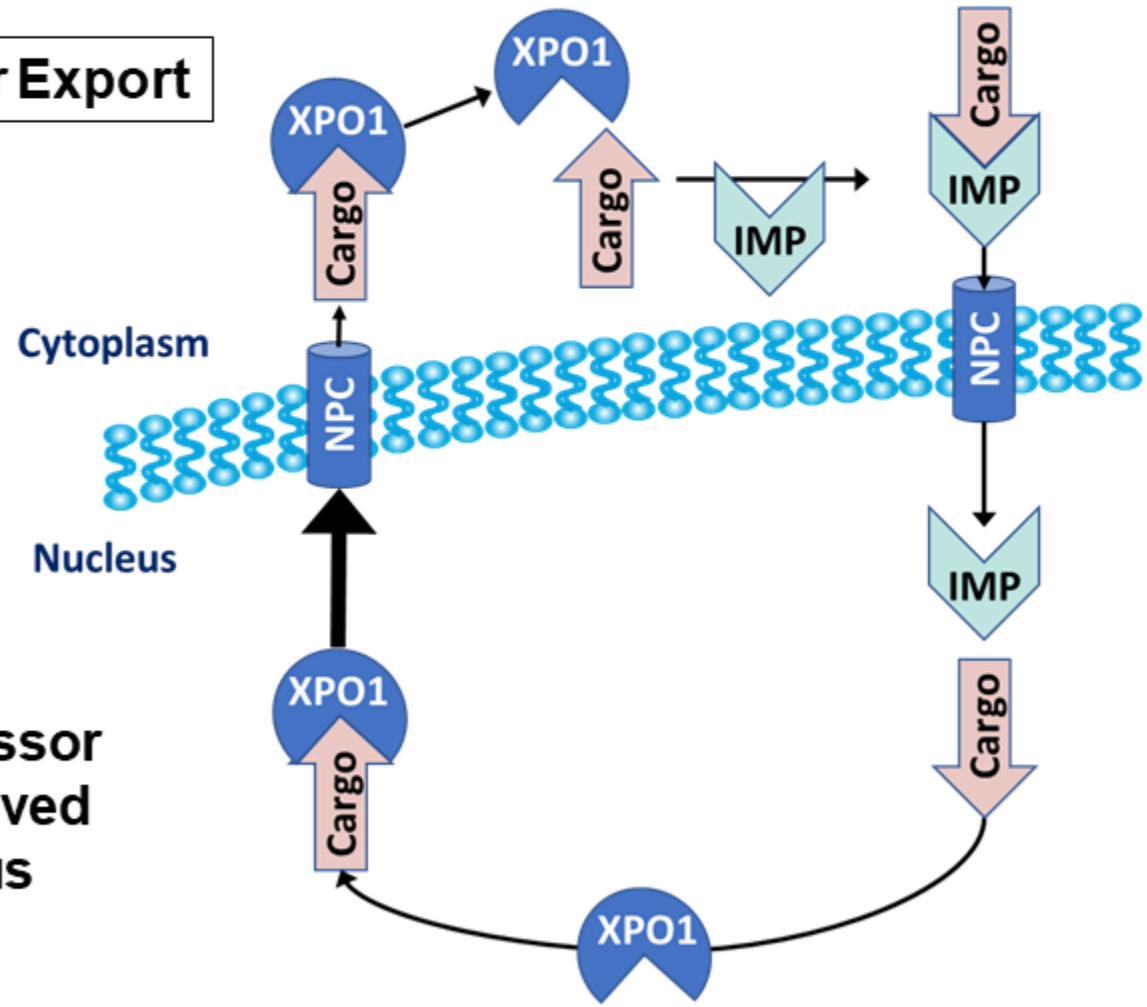
1. Usmani 2016; 2. Pick 2018

Selinexor Efficacy in Patients with Triple-class Refractory Multiple Myeloma

Jatin Shah, MD
Senior Vice President, Clinical Development
Karyopharm Therapeutics

Cancer Cells Utilize Nuclear Export to Remove Normal Control Mechanisms From Cell Nucleus

No Inhibition of Nuclear Export



Tumor suppressor proteins removed from nucleus

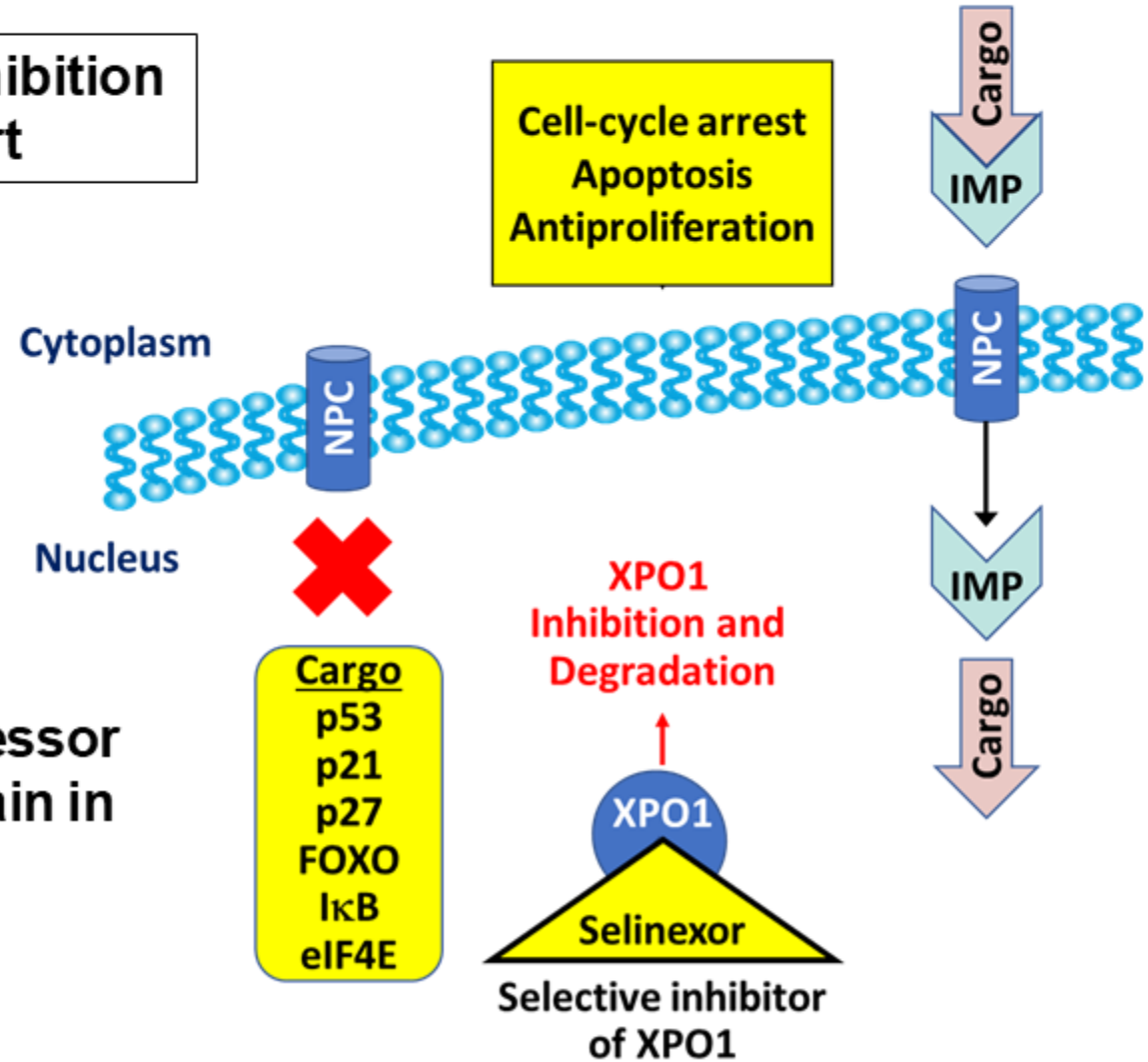
Legend

- XPO1 — Exportin 1
- IMP — Importin
- NPC — Nuclear pore complex

Xu 2010, Xu 2012, Gravina 2014, Tan 2014

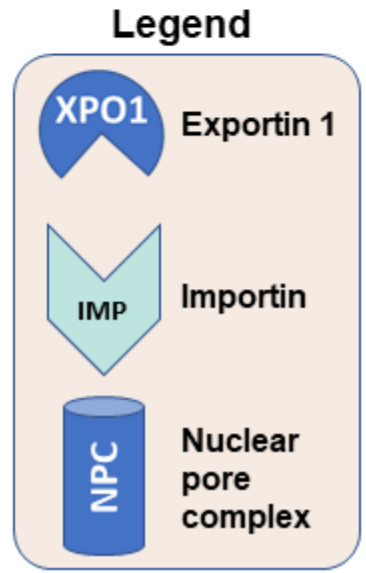
XPO1 Inhibition Forces Nuclear Accumulation and Activation of Tumor Suppressor Proteins (TSPs)

Selinexor Selective Inhibition of Nuclear Export



Selinexor upregulates glucocorticoid receptor expression and activity

Tumor suppressor proteins remain in nucleus



Xu 2010, Xu 2012, Gravina 2014, Tan 2014

Study 001 (N=81): Selinexor Monotherapy Induced Stable Disease and Minimal Response

- Phase 1 dose ranging study
- Heavily pre-treated patients with refractory MM and progressive disease at baseline
- 35 patients treated with selinexor monotherapy
  - 57% achieved stable disease or minimal response
- Supported evaluation in combination with dexamethasone

Selinexor 80 mg + Dexamethasone 20 mg Twice Weekly Provides Best Response with Manageable Tolerability

- Study 001 (Phase 1) established recommended dose[1]

Selinexor Dose Cohort (Fixed Dose)	n	Stable / Progressive Disease	Clinical Benefit Rate (MR+ORR)	Overall Response Rate (CR+VGPR+PR)
60 mg (35 mg/m^2) + dexamethasone	**7**	**3 (43%)**	**4 (57%)**	**0**
80 mg (45 mg/m^2) + dexamethasone	**12**	**4 (33%)**	**8 (67%)**	**6 (50%)**

1. Chen, 2017

STORM Part 2: Phase 2b, Open-label, Single-arm Study

- Selinexor 80 mg + dexamethasone 20 mg twice weekly
- Enrollment as early as 2 weeks since last therapy
- Objective response by Independent Review Committee (IRC)
  - International Myeloma Working Group criteria[1]

1. Kumar, 2016

STORM Part 2 Endpoints

- Primary endpoint
  - Overall response rate (ORR)
- Secondary endpoints
  - Duration of response (DOR)
  - Clinical benefit rate (CBR)
    - ≥ 25% reduction in disease burden
  - Overall survival (OS)

STORM Part 2: Broad Enrollment Criteria Allowed for Enrollment of Older and High-risk Patients

- No upper age limit (included patients > 75 years of age)
- Moderate-to-severe renal dysfunction
- Hematopoietic function with up to Grade 2 cytopenia
  - ANC ≥ 1,000/mm^3
  - Platelets ≥ 75,000/mm^3 or ≥ 50,000/mm^3 if 50% marrow plasmacytosis
- Permitted prior infections, thromboembolism, heart disease, and concomitant medications

STORM Part 2: Baseline Demographics Represent Real-world Patients

Patients with Triple-class Refractory Multiple Myeloma	STORM Part 2 (N=122)
Median Age; years (range)	65 (40 – 86)
≤ 75 years	85%
> 75 years	15%
Male	58%
Race	
White	70%
Black or African American	17%
Other	13%
Country	
US	69%
Outside US	31%

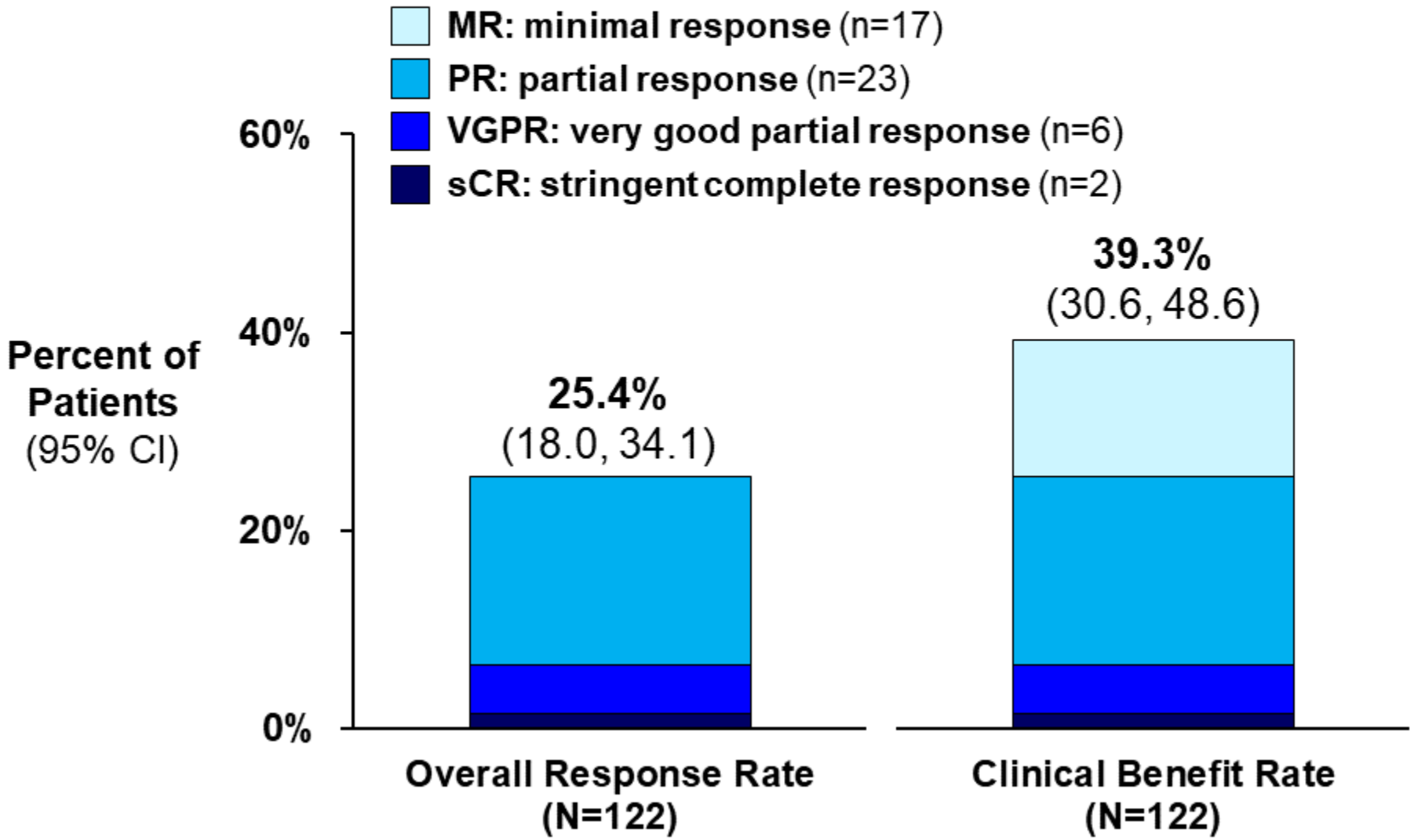
STORM Part 2: Heavily Pretreated Patients with Triple-class Refractory Multiple Myeloma

	STORM Part 2 (N=122)
Refractory to PI, IMiD, and daratumumab	100%
Refractory to glucocorticoid, including dexamethasone	100%
Refractory to prior glucocorticoid regimens, median	6
Time since diagnosis, median	6.6 years
Prior treatment regimens, median (range)	7.0 (3 - 18)
High-risk cytogenetics [del(17p)/p53, t(4;14), t(14;16), 1q21]	53%

STORM Part 2: Patients with Triple-class Refractory MM had Rapidly Progressing Disease

- 22% median increase in myeloma markers in 12 days between screening and first selinexor dose
- Marked tumor growth drives urgency to achieve rapid disease control

STORM Part 2: Primary Endpoint Demonstrates Meaningful Activity in Patients with Triple-class Refractory MM

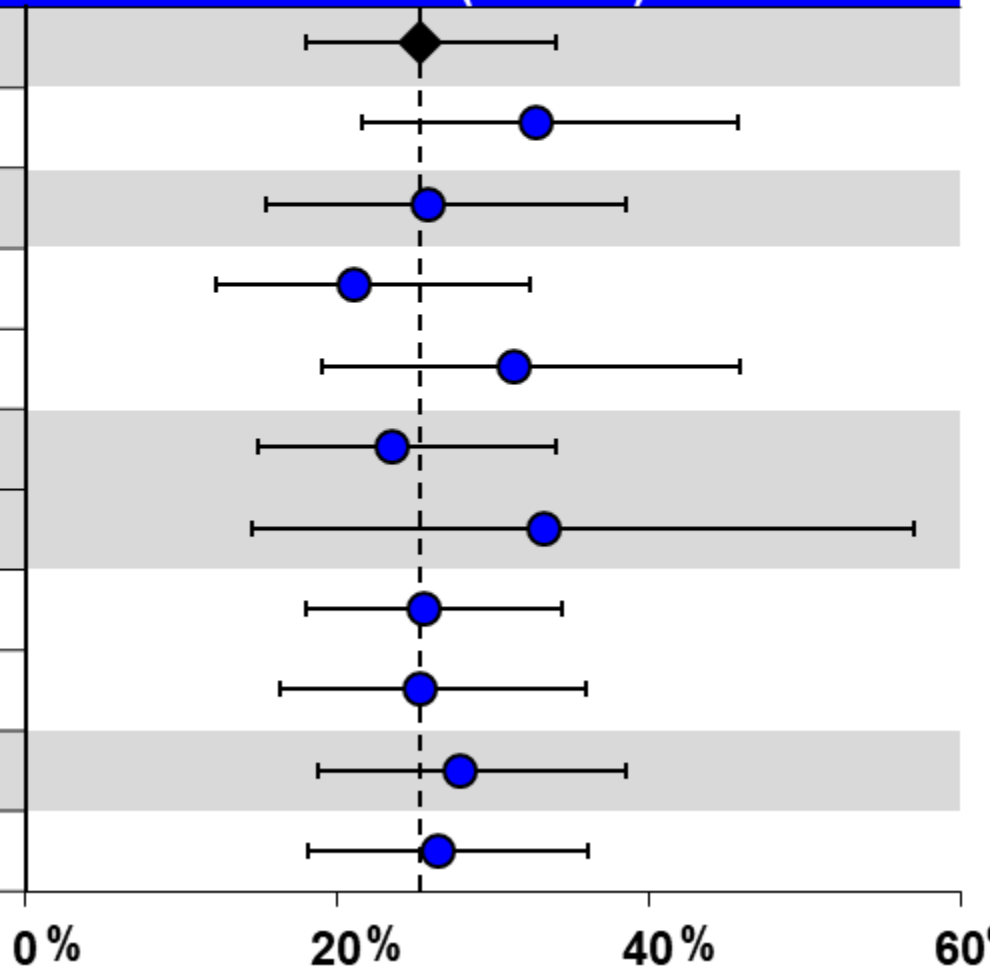


STORM Part 2: Best Response with Selinexor 80 mg + Dexamethasone 20 mg Twice Weekly

Average Weekly Selinexor Dose During Cycle 1	N	Overall Response Rate	Clinical Benefit Rate
160 mg/week (80 mg twice-weekly)	**56**	**18 (32.1%)**	**25 (44.6%)**
> 120 and < 160 mg/week	**14**	**4 (28.6%)**	**7 (50.0%)**
≤ 120 mg/week (≤ 60 mg twice-weekly)	**52**	**9 (17.3%)**	**16 (30.8%)**

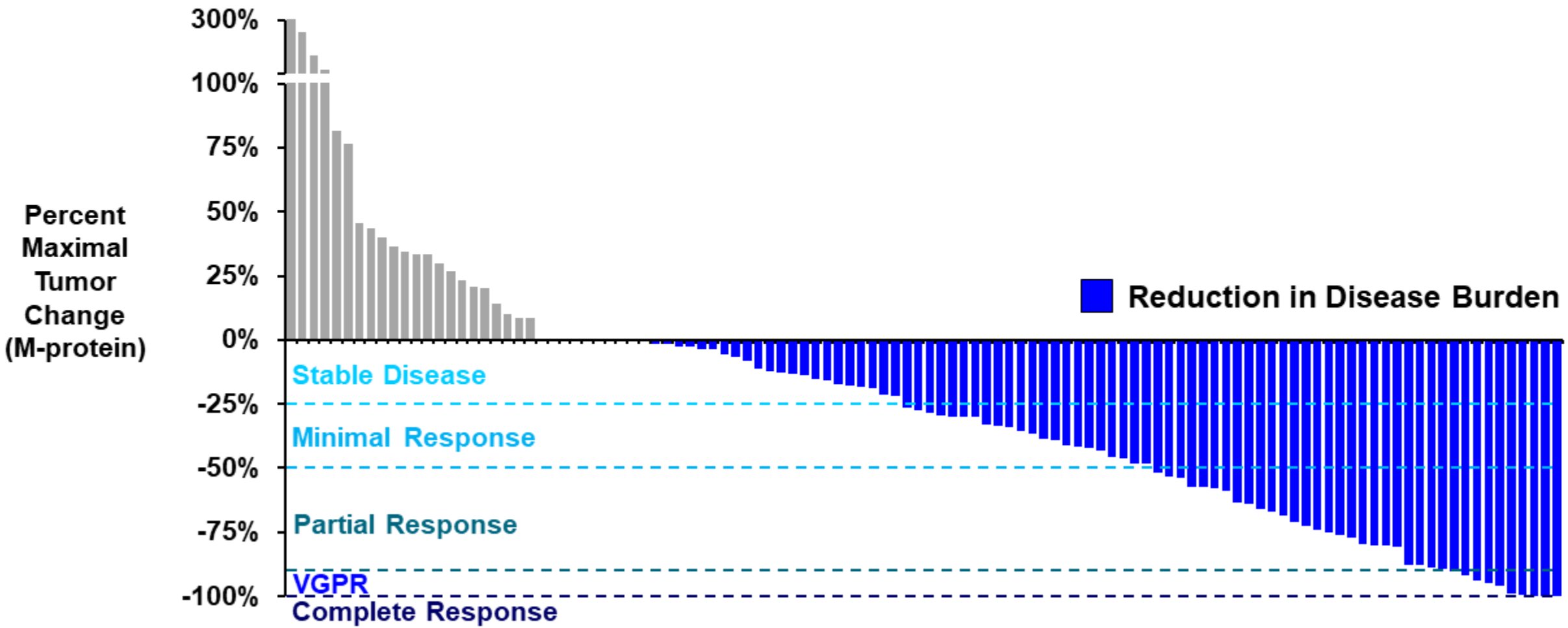
STORM Part 2: Consistent Overall Response Rate Across Patient Subgroups

	N	ORR (95% CI)
Overall	122	
Selinexor 1st therapy post PE-TCR	64	
Age > 65 years	62	
Male	71	
Female	51	
White	85	
Black or African American	21	
CPD-refractory	117	
BCLPD-refractory	83	
Daratumumab combination therapy	86	
Stem cell transplant	102	

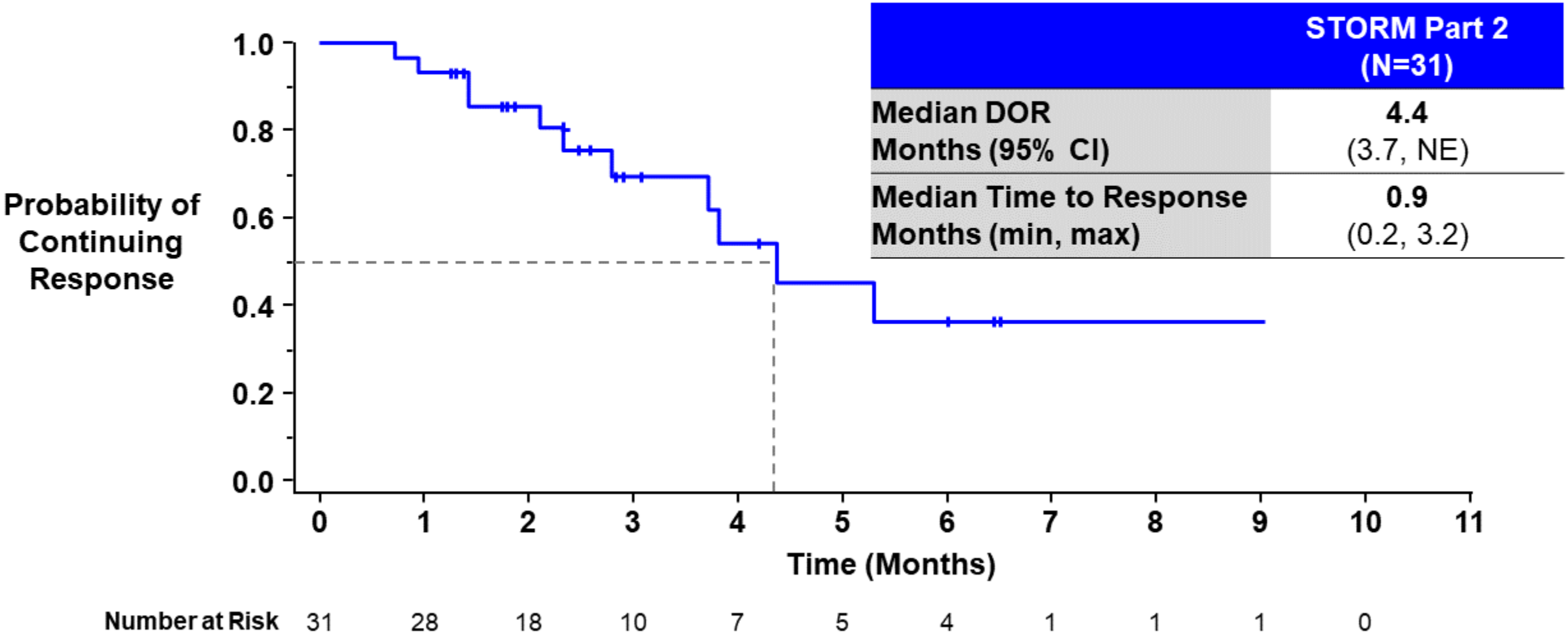


PE-TCR: penta-exposed, triple-class refractory
CPD: carfilzomib, pomalidomide, daratumumab
BCLPD: bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab

STORM Part 2: 71% of Patients had Reduction in Disease Burden



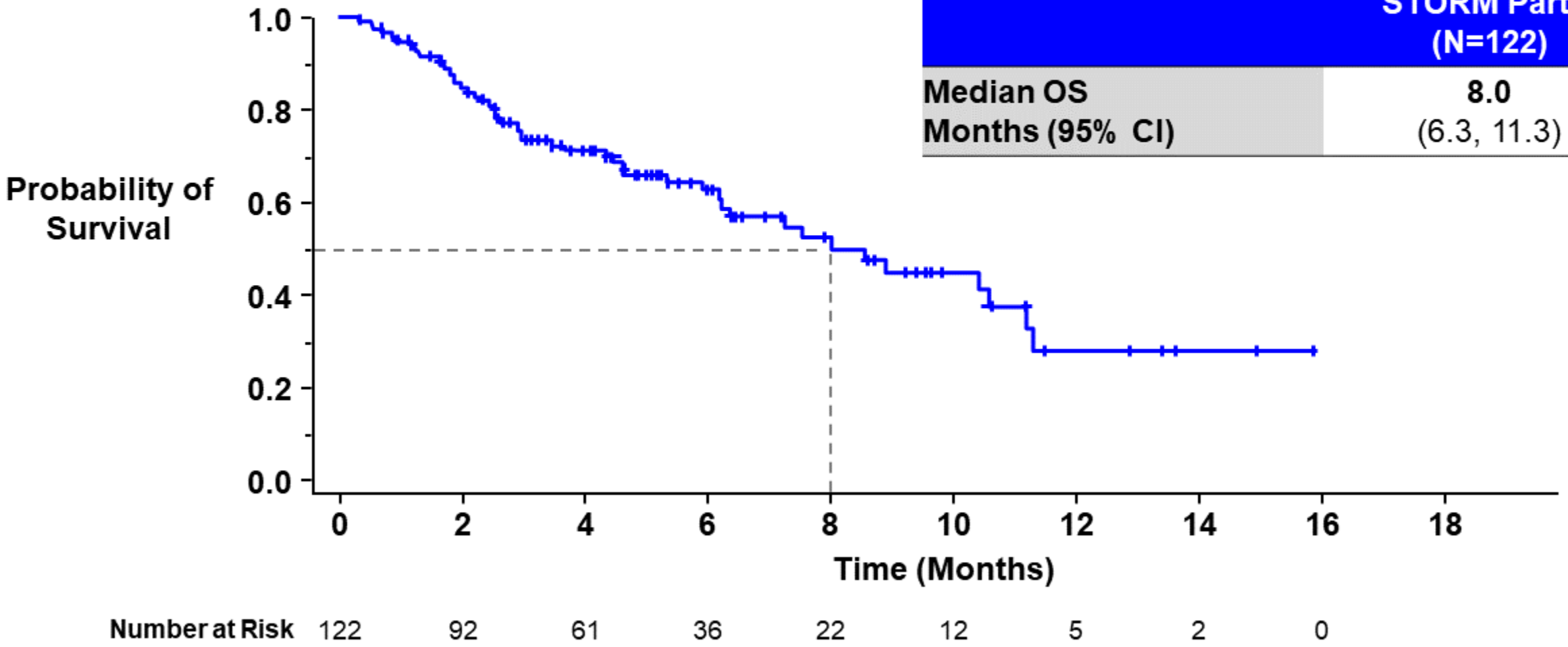
STORM Part 2: Demonstrated 4.4-month Duration of Response



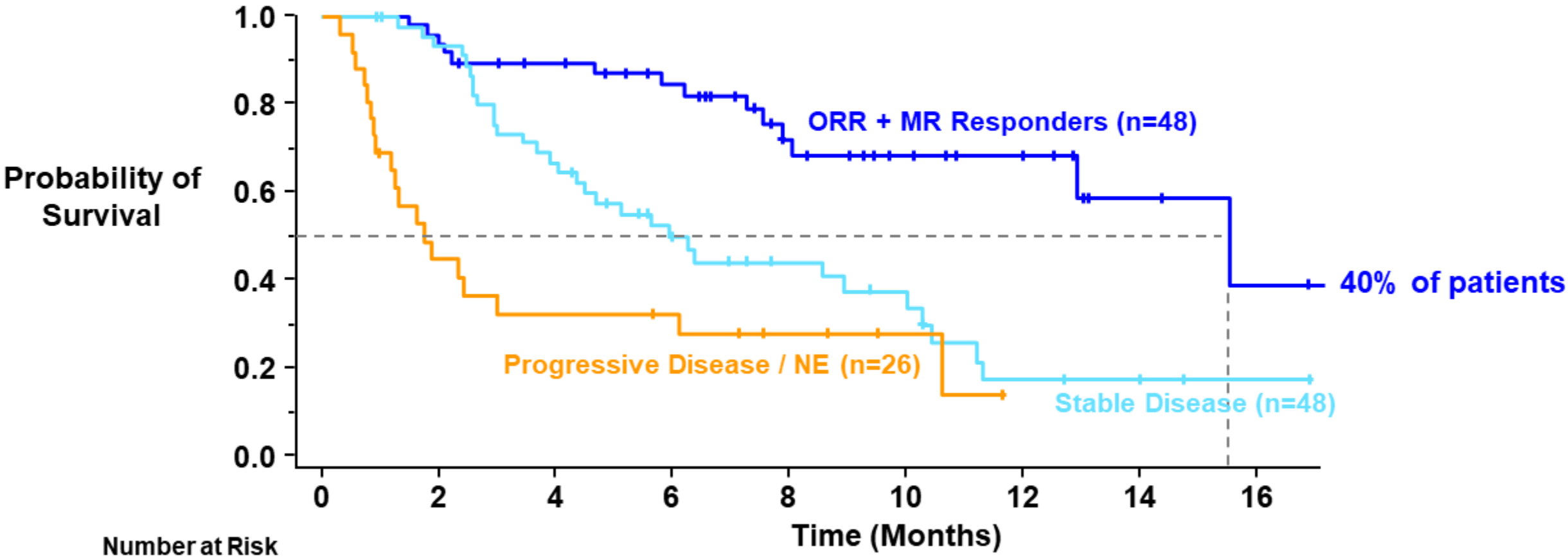
	STORM Part 2 (N=31)
Median DOR Months (95% CI)	**4.4** (3.7, NE)
Median Time to Response Months (min, max)	**0.9** (0.2, 3.2)

STORM Part 2: 8-month Median Overall Survival

	STORM Part 2 (N=122)
Median OS Months (95% CI)	8.0 (6.3, 11.3)



STORM Part 2: Overall Survival by Response



Number at Risk									
ORR + MR Responders	48	46	40	33	19	13	10	4	2
Stable Disease	48	42	30	19	13	10	4	3	1
Progressive Disease	26	11	8	7	4	2			

Continued Selinexor Benefit Observed with 90-Day Efficacy Update

	STORM Part 2 (N=122)	
	Submission	90-Day Update
Overall Response Rate	25.4%	26.2%
Clinical Benefit Rate	39.3%	39.3%
Duration of Response, months	4.4	4.4
Overall Survival, months	8.0	8.6

Selinexor Depth of Response Comparable to Therapies Using Accelerated Approval Pathway

Therapy	Refractory Class	Sample Size	ORR	sCR/CR	VGPR	PR
Carfilzomib[1]	Single	266	22.9%	0.4% n=1	4.9% n=13	17.7% n=47
Pomalidomide[2] + low-dose dexamethasone	Single and Double	113	29.2%	0.9% n=1	0% n=0	28.3% n=32
Daratumumab[3]	Double	106	29.2%	2.8% n=3	9.4% n=10	17.0% n=18
Selinexor[4] + low-dose dexamethasone	Triple	122	26.2%	1.6% n=2	4.9% n=6	19.7% n=24

1. Kyprolis USPI (2018); 2. Pomalyst USPI (2018); 3. Darzalex USPI (2018); 4. Selinexor 90-day update

Demonstrated Efficacy in Patients with Triple-class Refractory Multiple Myeloma

- Clinically meaningful response rate
  - Rapidly progressing disease
  - Demonstrated Overall Survival (OS) of 8.6 months in a population with expected OS of 3.5 to 5.6 months

Selinexor Safety

Michael Kauffman, MD, PhD
CEO and Chief Medical Officer
Karyopharm Therapeutics

Physicians Able to Prevent, Monitor, and Manage Treatment-emergent Events

- Dose modifications and/or supportive care alleviate symptoms
- AEs generally reversible
- Major organ toxicities not prominent

Selinexor Evaluated in 1116 Patients with Advanced, Heavily Pretreated, Hematological Malignancies

	Selinexor N
Hematological malignancies (MM, NHL, AML)	1116
MM treated with selinexor + dexamethasone regimen[1]	214
STORM Part 2[1]	123

1. Selinexor 80 mg + dexamethasone 20 mg taken orally twice weekly

AML=acute myeloid leukemia; MM=multiple myeloma; NHL=non-Hodgkin lymphoma

Study 008 (AML): Not Informative to Approval of Selinexor in Triple-class Refractory Myeloma

- Exploratory Phase 2 study in different tumor type
- Compared single agent selinexor against active standard of care anti-AML therapies
- No significant difference in infections or AEs leading to death

STORM Part 2: Enrolled Patients had Many Comorbidities at Baseline

		STORM Part 2 (N=123)
Median Comorbidities at Baseline		**N=10**
Hematologic	Anemia	91%
	Thrombocytopenia	36%
Non-hematologic	Cataracts	51%
	Peripheral neuropathy	43%
	Hypertension	39%
	Back pain	29%
	Cardiac disorders	28%
	Fatigue	23%

Peripheral neuropathy includes peripheral sensory and neuropathy peripheral
Anemia and thrombocytopenia based on lab values at baseline
Cataract based on screening ophthalmological examination

STORM Part 2: Summary of Adverse Events

	STORM Part 2 (N=123)
Time since diagnosis, median	**6.6 years**
Median prior treatment regimens (range)	**7** (3-18)
AEs Grade 3 and 4	**94%**
AEs leading to discontinuation	**27%**
SAEs	**60%**
AEs leading to death	**8%**

STORM Part 2: Similar SAE Rates in Patients with Less Heavily Pretreated MM

	STORM Part 2 Selinexor + Dex[1] (N=123)	Pomalidomide[2] (N=107)	Pomalidomide + Low-dose Dex[2] (N=112)	Carfilzomib[3] (N=266)	Carfilzomib[4] (N=157)
Prior treatment regimens, median	7	5	5	5	5
PI and IMiD refractory	100%	59%	62%	80%*	62%
SAEs	60%	67%	62%	47%	59%
AEs leading to death	8%	7%	5%	4%	10%

* Refractory or intolerant to bortezomib and lenalidomide

1. Selinexor 80 mg and dexamethasone 20 mg taken orally twice weekly; 2. FDA SBA, 2013; 3. Siegel, 2012; Onyx ODAC Briefing Book, 2012; 4. Hajek, 2017 (not submitted for FDA approval)

STORM Part 2: Most Commonly Reported Hematologic AEs

Preferred Term	STORM Part 2 (N=123)		
	All Grades	Grade 3	Grade 4
Thrombocytopenia	**73%**	**27%**	**32%**
Concurrent Grade 3 and 4 bleeding*	0	4%	0
Anemia	**66%**	**42%**	**1%**
Neutropenia	**38%**	**19%**	**3%**
Febrile neutropenia	2%	2%	0

*Defined as a concurrent event within the hemorrhage SMQ occurring within 5 days from the onset of the event of thrombocytopenia

STORM Part 2: Most Commonly Reported Non-hematologic AEs

		STORM Part 2 (N=123)		
	Preferred Term	All Grades	Grade 3	Grade 4
Non-hematologic	Nausea	70%	10%	*NA*
	Fatigue	63%	20%	*NA*
	Decrease appetite	54%	4%	0
	Weight decreased	49%	0	*NA*
	Diarrhea	42%	7%	0
	Vomiting	37%	3%	0
	Hyponatremia	35%	20%	1%

NA=not applicable; not defined in CTCAE

STORM Part 2: Dose Modifications Effective for Reducing Discontinuations

		STORM Part 2 (N=123)	
	Preferred Term	AE Leading to Dose Modification	AE Leading to Discontinuation
Hematologic	Thrombocytopenia	44%	3%
	Neutropenia	11%	0%
	Anemia	6%	2%
Non-hematologic	Fatigue	16%	4%
	Nausea	9%	6%
	Weight decreased	6%	4%
	Decreased appetite	5%	2%
	Hyponatremia	5%	0%
	Vomiting	3%	2%

STORM Part 2: SAEs

		STORM Part 2 (N=123)	
	Preferred Term	Any SAE	Any Treatment-related SAE
Hematologic	Anemia	3%	< 1%
Non-hematologic	Pneumonia	11%	3%
	Sepsis	9%	2%
	Mental state changes	4%	0
	Fatigue	3%	2%
	General physical health deterioration	3%	2%

STORM Part 2: Progressive Disease Most Commonly Reported Cause of Death

Preferred Term	STORM Part 2 (N=123)	
	Any Death	
	N	%
Progressive disease	13	10.6%
Sepsis	4	3.3%
Pneumonia	2	1.6%
Multi-organ dysfunction	1	0.8%
Subdural hematoma	1	0.8%
Cardiac disorder	1	0.8%
Respiratory arrest	1	0.8%

Management of Common Adverse Events

MM Population: Prophylactic Olanzapine and/or Megesterol Reduces Percent of Patients With AEs

Adverse Event	Any Adverse Event	
	No Prophylactic Supportive Care (N=312)	With Prophylactic Supportive Care (N=39)
Nausea / vomiting, fatigue, anorexia	87%	64%
Nausea / vomiting	67%	46%
Fatigue	60%	44%
Anorexia	47%	28%

Monitoring Important to Prevent and Manage AEs

- Weekly monitoring for first 8 weeks of treatment
  - Routine CBC and basic serum chemistry
  - Body weight
- At least monthly monitoring after first 8 weeks
  - Based on clinical situation

Recommended Supportive Care and Dose Modifications for Thrombocytopenia with Selinexor

Severity	Supportive Care	Dose Modification
Grade 3 (without bleeding)	**Platelet transfusions and consider thrombopoietin agonists**	**100 mg once weekly**
Grade 3 with bleeding or Grade 4		**Withhold selinexor** (until return to Grade ≤ 2) **100 mg once weekly**

- Reduce selinexor dose by 20 mg for each subsequent event

Recommended Supportive Care and Dose Modifications for AEs Associated with Selinexor

Non-hematologic AE Preferred Term	Supportive Care	Dose Modification
Nausea / vomiting	Olanzapine, megesterol, hydration	Withhold 1 dose
Fatigue		Decrease by 20 mg Continue with twice weekly
Decreased appetite		

5 Key Education and Monitoring Actions to Support Selinexor Use

Action	Activities
Educate and Support HCP	• Nurse liaison team • AE management guidelines and peer-reviewed publications
Educate and Support Patient	• Discussion of benefit-risk, and advise on management of expected AEs • 24/7 specialty pharmacy network with oncology-trained nurses • Myeloma advocacy groups
Monitor for AEs	• Monitoring of CBC, basic serum chemistry, body weight • Weekly during first 8 weeks and then at least monthly • Specialty pharmacies report AEs to HCPs
Manage AEs	• Dose reduction or interruption for Grade ≥ 3 hematological events and Grade ≥ 2 non-hematological events • Supportive care (prophylaxis and as needed)
Stopping Criteria	• Confirmed disease progression in 1-2 months • Significant AEs despite dose modifications and supportive care

Well-defined Side Effects Manageable and Generally Reversible

- Common AEs: thrombocytopenia, nausea/vomiting, fatigue, decreased appetite
- Bleeding events and severe infections are uncommon
- Common non-hematologic AEs, mainly Grade 1 or 2
  - Not associated with significant major organ toxicities
- Mitigation strategies communicated to healthcare providers and patients

Clinical Perspective

Sundar Jagannath, MD
Director, Multiple Myeloma Program
Professor of Medicine
Tisch Cancer Institute at Mount Sinai School of Medicine

No Approved Drugs Once Disease Becomes Refractory to Key Anti-myeloma Therapies

- Tried available options: daratumumab, PIs, and IMiDs
  - Start recycling same drugs in different combinations

Patients with Relapsed Refractory MM Older With Comorbidities and Poly-pharmacy

- Present at advanced stage of myeloma
- High symptom burden from myeloma, prior therapies, other medical problems
  - Peripheral neuropathy, renal and liver function decline
  - Cardiac compromise
- Poor prognosis, significant disease burden, short survival
- Small window to achieve disease control, clinical response

Oral Selinexor: New Therapeutic Class with Novel Mechanism of Action

- First agent evaluated in patients with triple-class refractory, rapidly progressing multiple myeloma
- Different side effect profile
  - Low risk for peripheral neuropathy, renal toxicity, hepatic toxicity, or cardiovascular side effects
- Infection rate consistent with studies in heavily pretreated MM
- Median OS of 15.6 months in patients with ≥ MR highlights favorable benefit-risk ratio

Clinically Meaningful Responses in Heavily Pretreated Patients

- Clinically meaningful 26.2% response rate, duration of response

	Patient 1 Stringent Complete Response	Patient 2 Very Good Partial Response
Age / Gender	65 / Female	58 / Male
Prior lines (n)	8	6
After selinexor	VGPR on Day 15 sCR on Day 113	Creatinine: 3.94 → 2.52 Free light chain: 12,000 → 664
Best response	MRD negative by Month 4	VGPR

- 21 of 39 patients with moderate to severe renal dysfunction at baseline, improved at end of study

Initiate Selinexor at Recommended Dose to Rapidly Halt Disease

- Expect dose modifications
- Anticipate adverse events
  - Supportive care effective for patients

Clinical Experience Gained in Managing AEs Shared to Improve Patient Outcomes

	N	Discontinuation Due to AE	ORR
mITT	**122**	**26.2%**	**25.4%**
High-enrolling sites (≥ 6 patients)	**71**	**22.5%**	**29.6%**
Other Sites (≤ 5 patients)	**51**	**31.4%**	**19.6%**

- Algorithms developed to manage side effects, to be communicated to physicians and staff

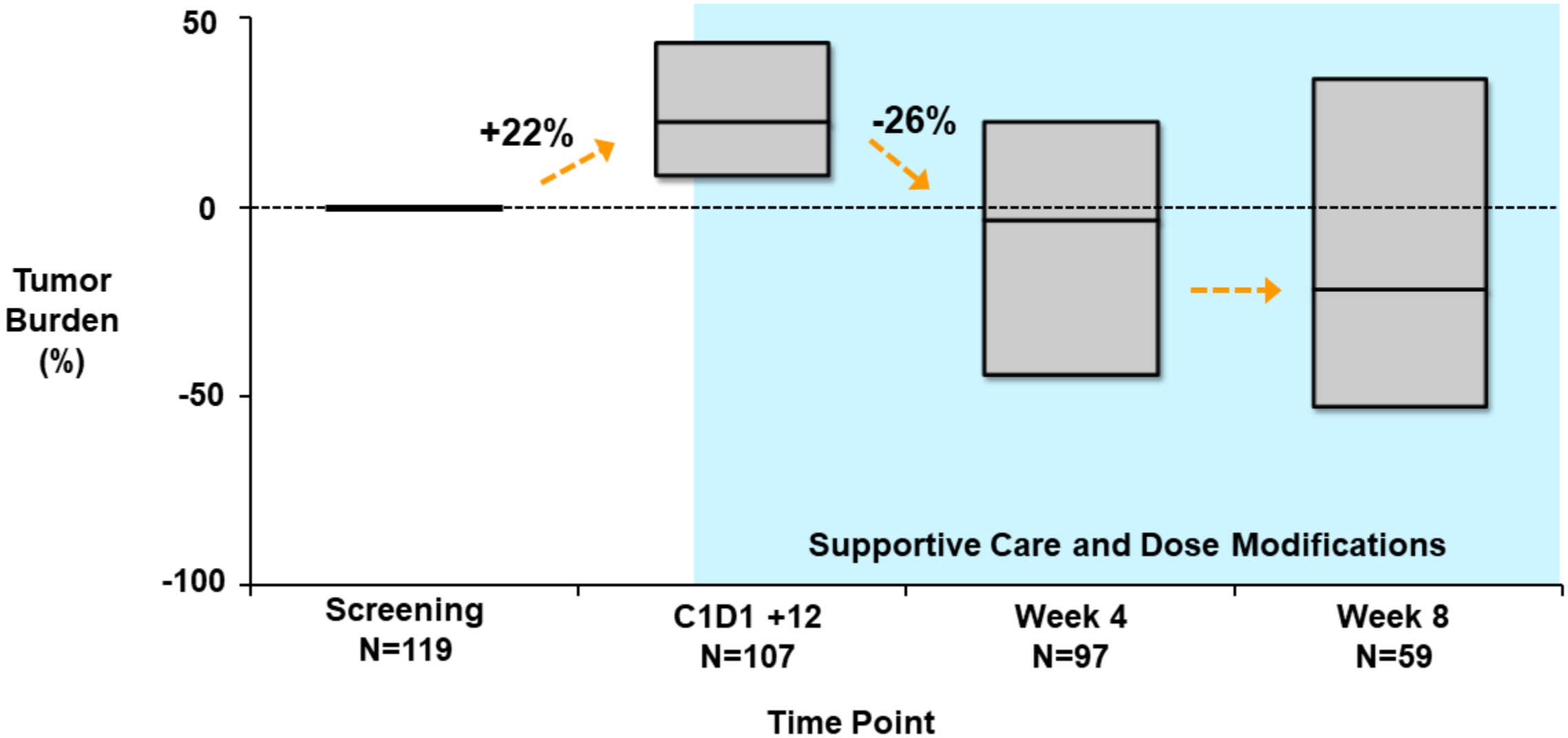
Urgent Need: Patients Need Effective Therapies Now

- Demonstrated benefits and ability to manage AEs
  - No need to wait
- Know enough to provide patients and physicians option to try this novel, effective therapy

Selinexor Positive Benefit-Risk Supports Accelerated Approval

Sharon Shacham, PhD
President and Chief Scientific Officer
Karyopharm Therapeutics

STORM Part 2: Rapid Disease Control and Dose Modifications for Optimal Benefit-Risk



Awaiting BOSTON Study Means Patients Would Not Have Access to Selinexor for ≥ 2 Years

Accelerated Approval Criteria	Selinexor Fulfills Criteria
Serious condition	✓ Short median OS in triple-class refractory MM
Meaningful advantage over available therapy	✓ No effective therapies ✓ ORR of 25.4% in triple-class refractory MM
Demonstrates effect on endpoint that is reasonably likely to predict clinical benefit	✓ ORR predicts for longer OS in patients with advanced MM ✓ ORR in triple-class refractory MM similar to accelerated approvals in single- or double-class refractory MM

Selinexor Positive Benefit-Risk for Triple-class Refractory Multiple Myeloma (MM)

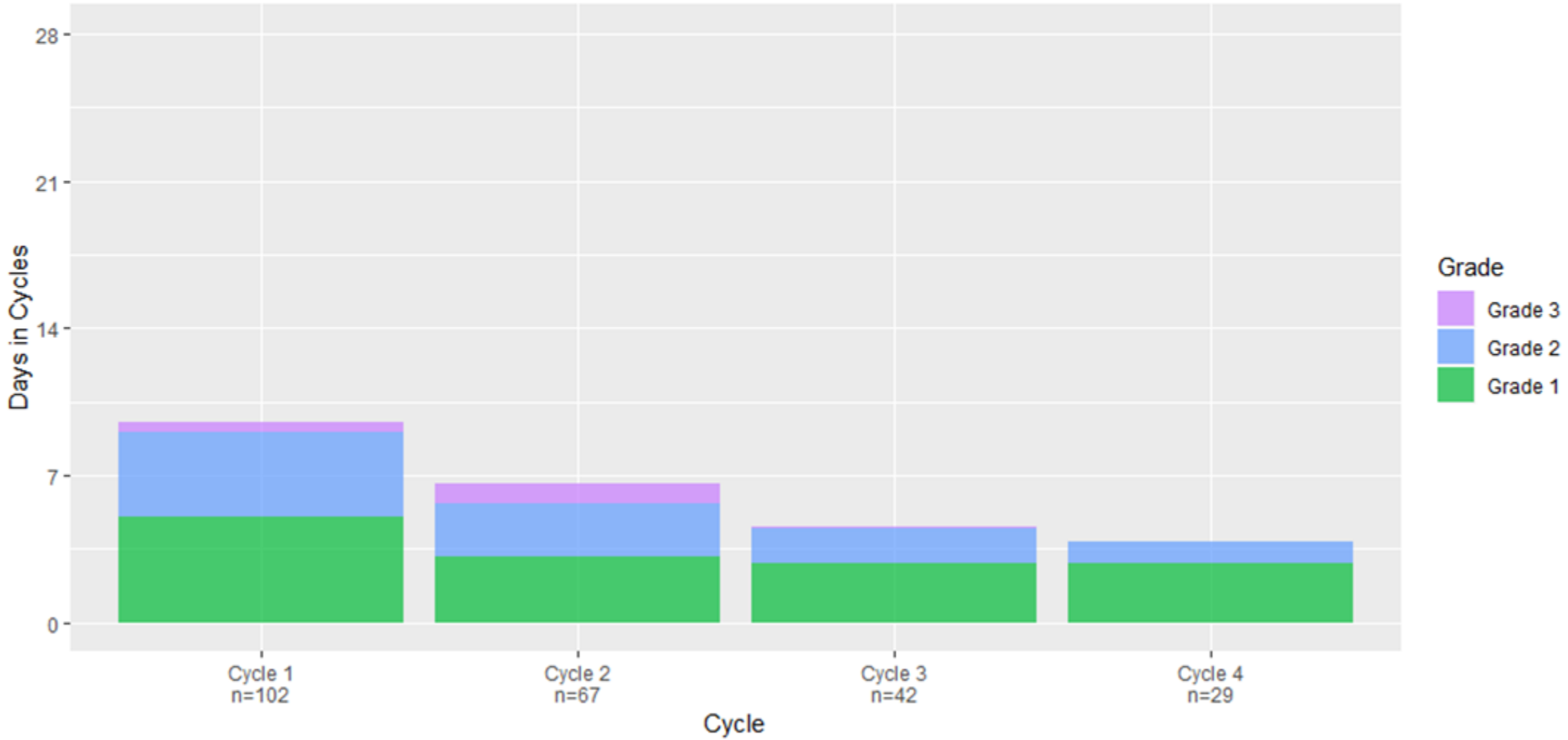
February 26, 2019

Karyopharm Therapeutics

Oncologic Drugs Advisory Committee

BACKUP SLIDES SHOWN

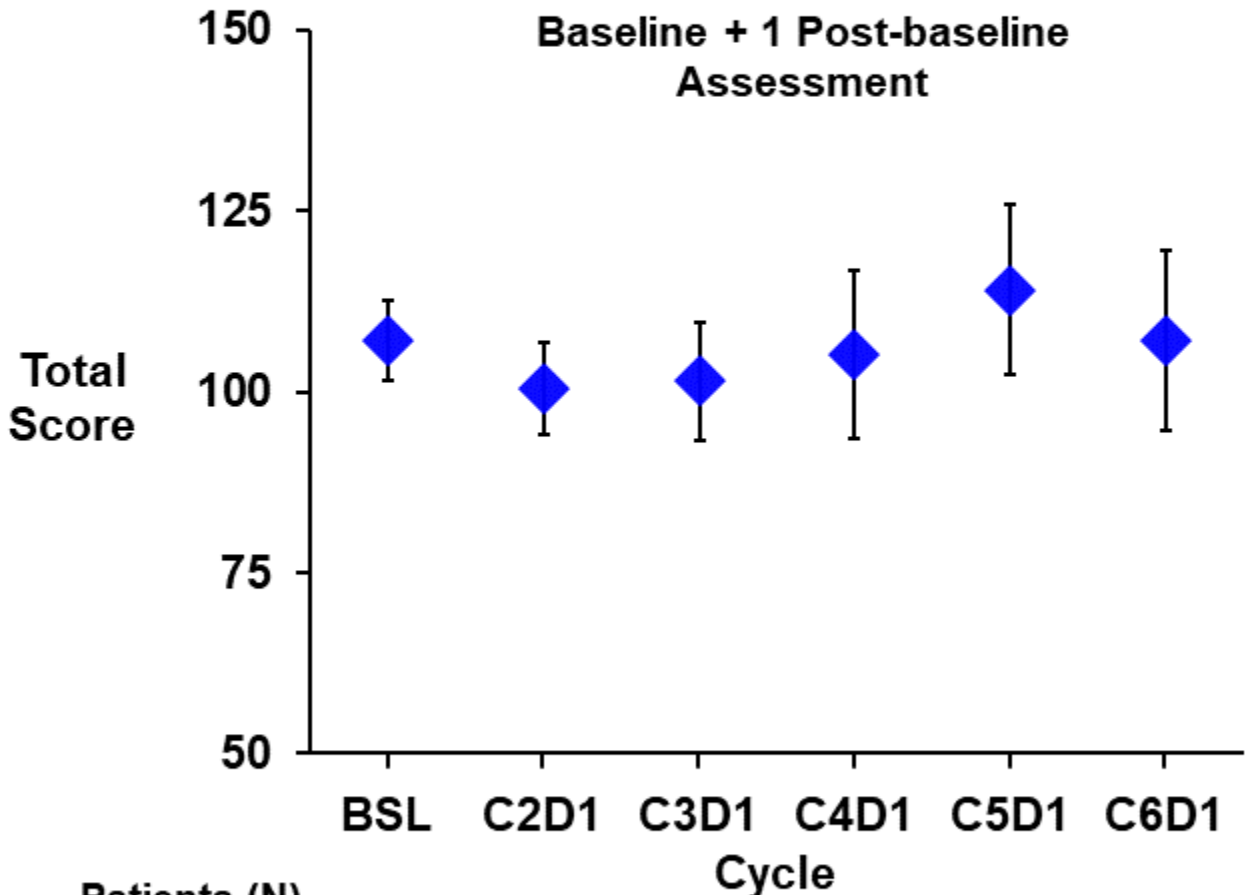
STORM Part 2: Number of Days Patients Experienced Nausea (by Grade)

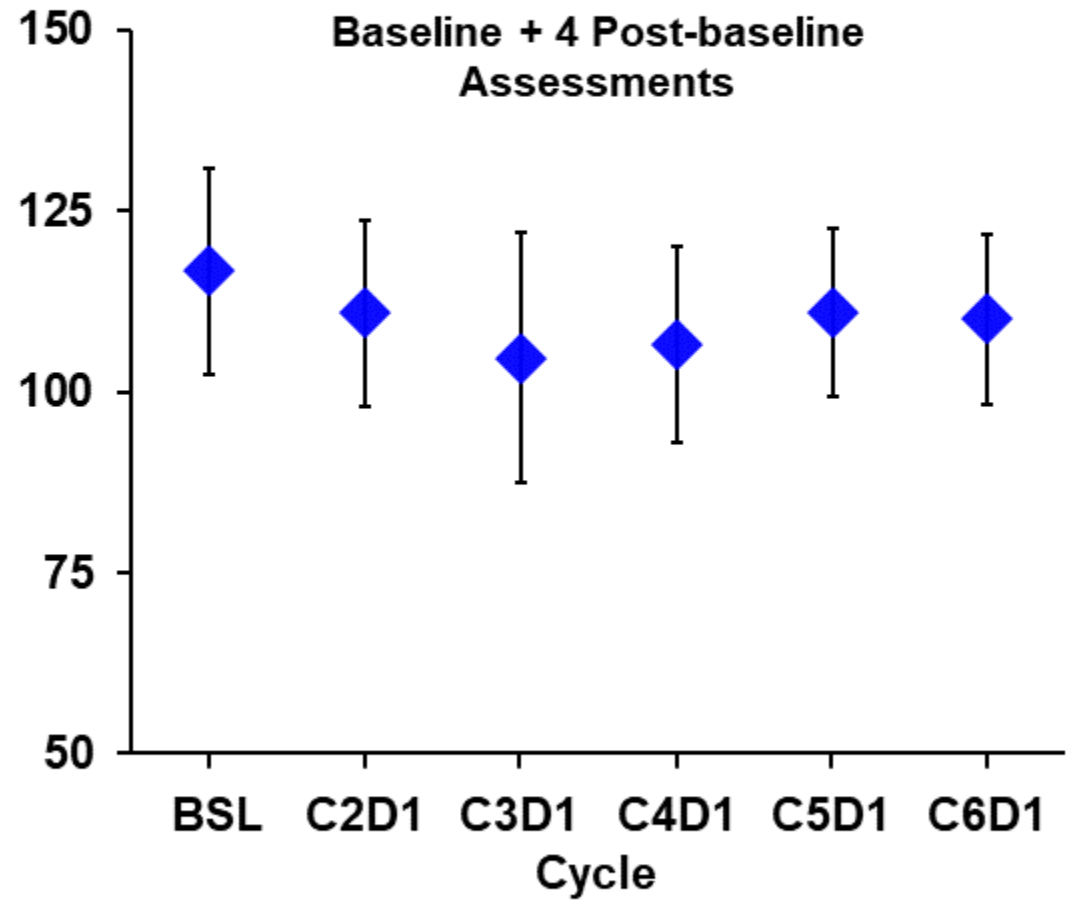


MM Population: Prophylactic Olanzapine and/or Megesterol Reduces Percent of Patients With AEs

Adverse Event	Any AE (%)		≥ Grade 2 AE (%)	
	No Prophylactic Supportive Care (N=312)	With Prophylactic Supportive Care (N=39)	No Prophylactic Supportive Care (N=312)	With Prophylactic Supportive Care (N=39)
Nausea/vomiting, fatigue, anorexia	87%	64%	65%	46%
Nausea/vomiting	67%	46%	34%	23%
Fatigue	60%	44%	44%	36%
Anorexia	47%	28%	23%	23%

Selinexor: No Apparent Negative Impact on Quality of Life (FACT-MM: Total Score)



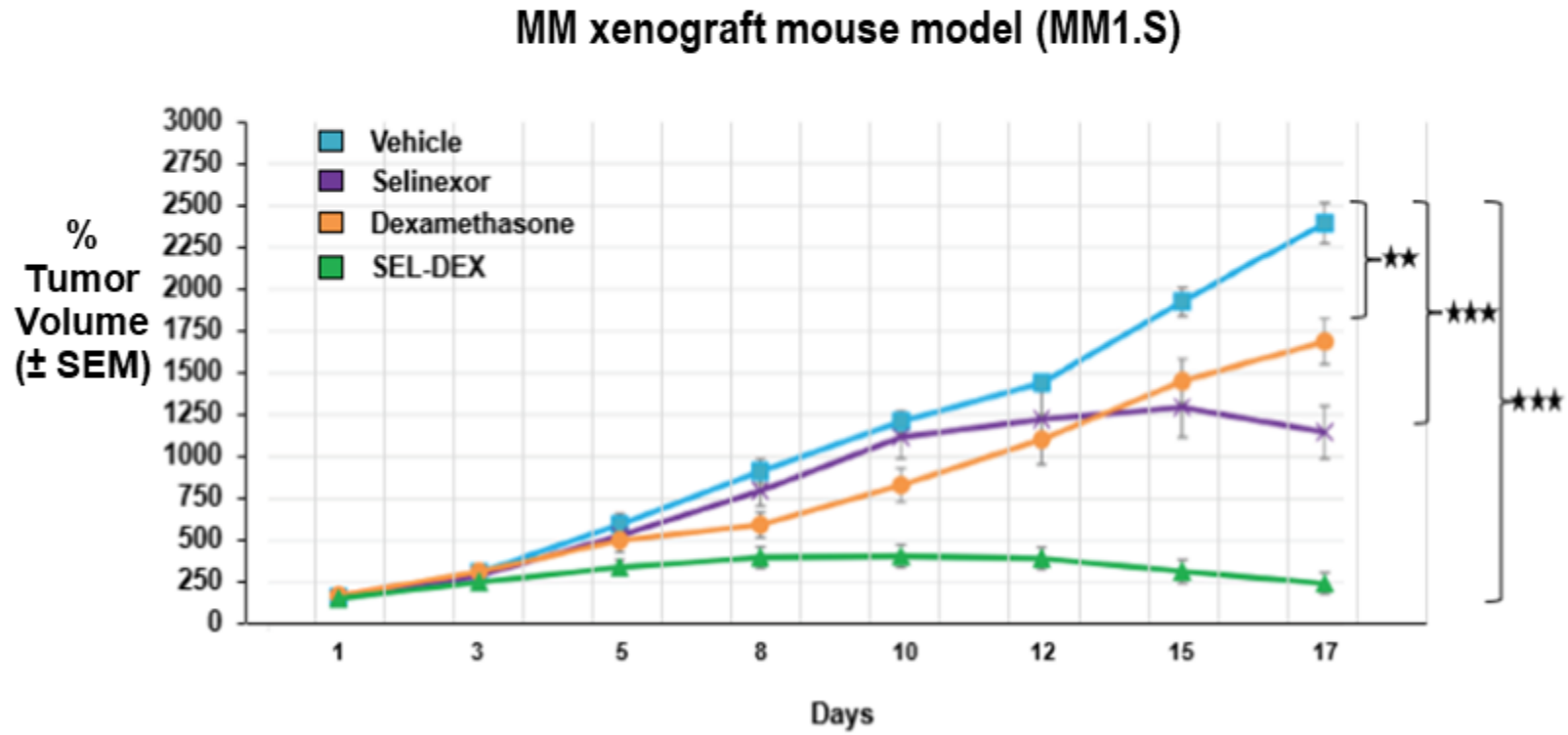


Patients (N)	BSL	C2D1	C3D1	C4D1	C5D1	C6D1
With assessment	83	75	47	27	20	16
On Study	122	90	60	39	27	18
With assessment	17	17	14	16	16	14
On Study	27	27	27	27	27	18

BSL = Baseline; C = Cycle; D = Day; FACT-MM: Functional Assessment Of Cancer Therapy - Multiple Myeloma

Selinexor Synergizes with Glucocorticoids to Induce Apoptosis of Multiple Myeloma Cells

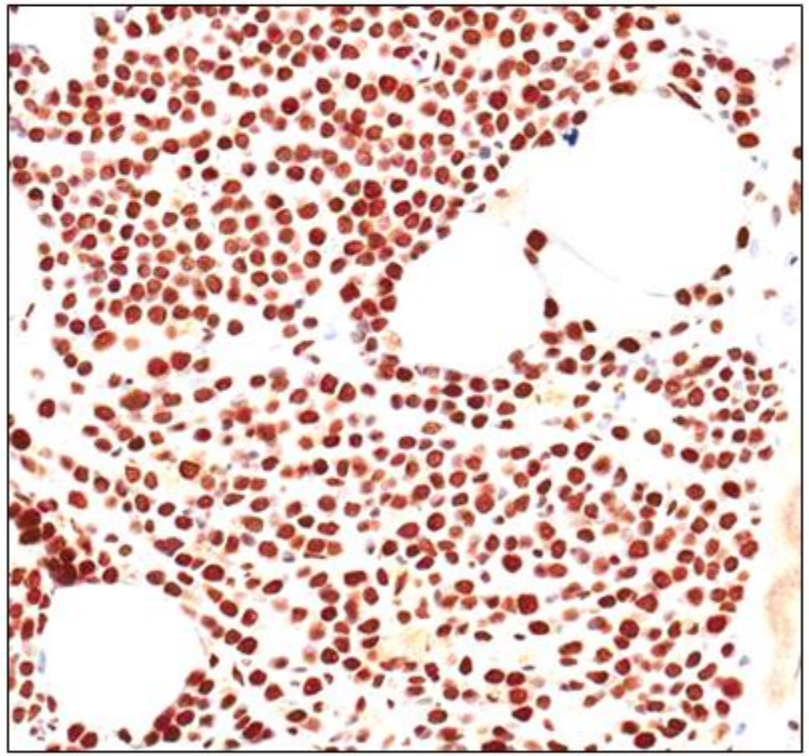
- In combination with dexamethasone, selinexor increases the glucocorticoid receptor (GR) expression and its transcriptional activity
- The GR transcriptional activity increases selinexor-mediated NFκb inhibition
- Only selinexor plus dexamethasone combination inhibits the mitogenic mTOR pathway



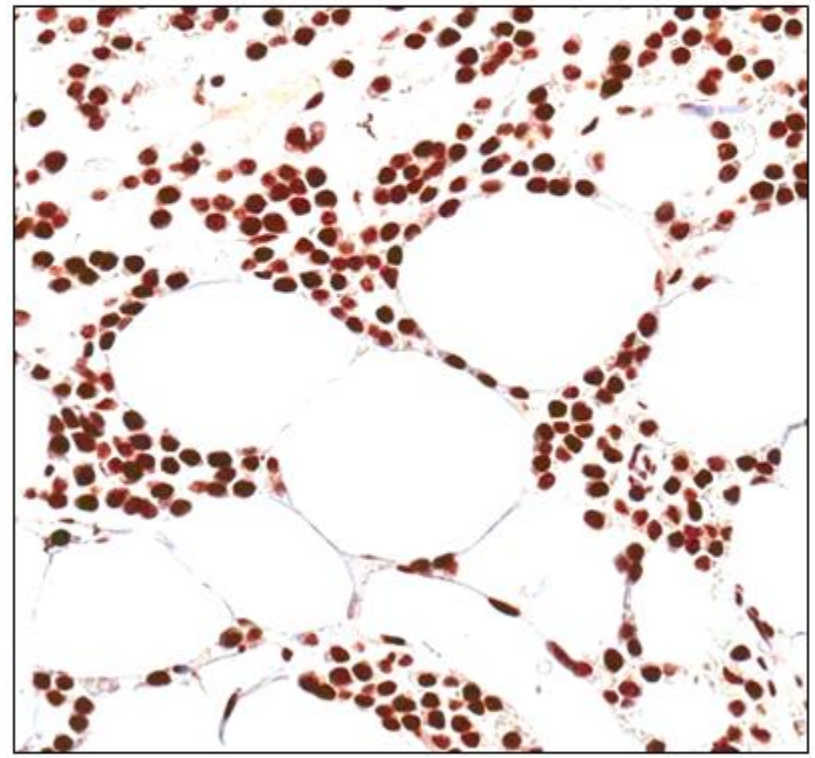
Argueta 2018

Patient's Biopsy Results Shows Synergetic Effect Between Selinexor and Dexamethasone

Baseline



Post-selinexor (C2D8)



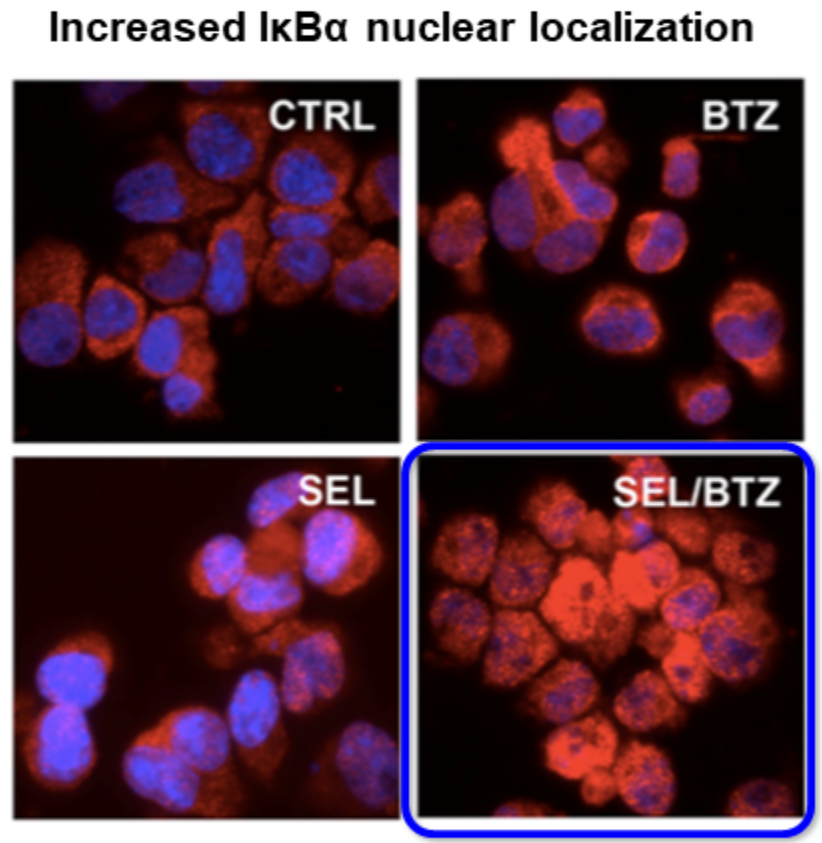
Dark brown = glucocorticoid receptor

Selinexor 45 mg/m^2 + Dexamethasone 20 mg

Patient's Response: PR

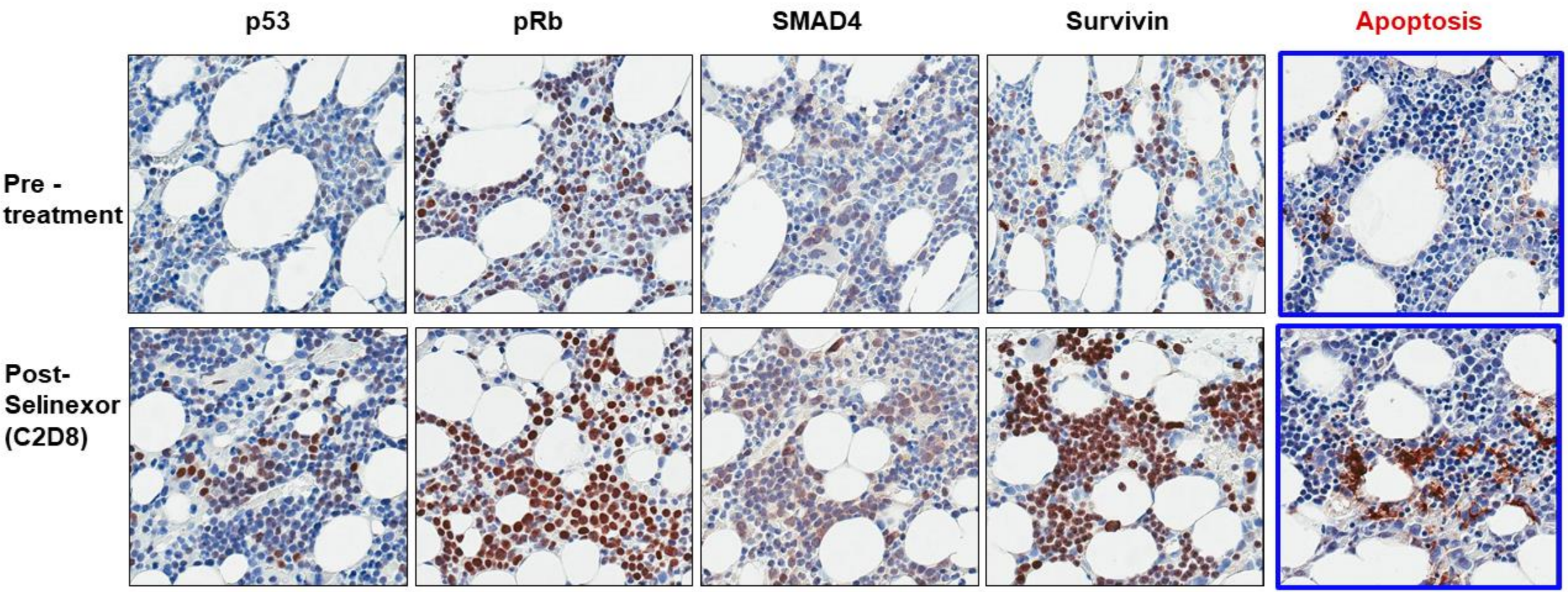
BOSTON: 100 mg Once Weekly (QW) Dose Rationale

- BOSTON study dosing: Selinexor: 100 mg QW + Bortezomib: 1.3 mg/m^2 QW SC + Dex: 20 mg
- Preclinical data has shown synergistic effect with protease inhibitor (bortezomib) and glucocorticoid receptor (dexamethasone)
- Selinexor 100 mg once weekly is the R2PD dose from phase 1 study:
  - High levels of anti-MM activity
  - Low AE rates and low levels of peripheral neuropathy



Turner et al. 2016

Selinexor Induces Nuclear Localization of TSP in Biopsy Sample from Patient with RR Multiple Myeloma



Chen et al 2018

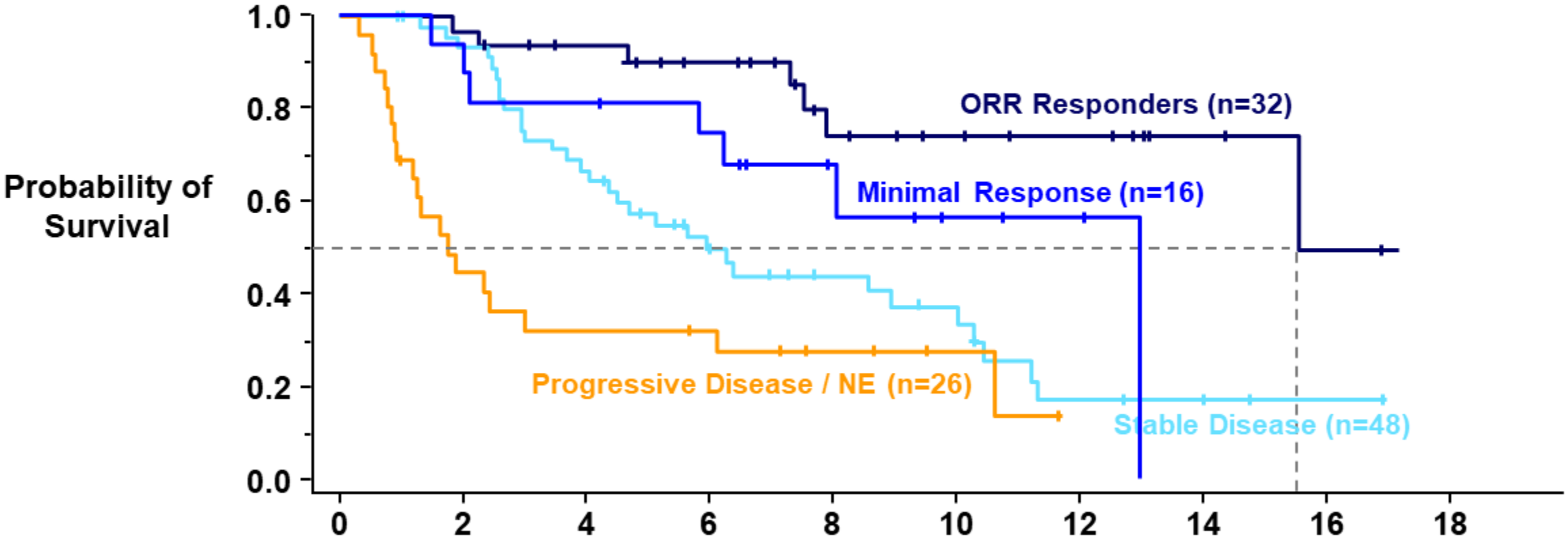
STORM Part 2: Overview of AEs by Age

Preferred Term	≤64 years n=60	65-74 years n=44	>75 years n=19	Total N=123
Thrombocytopenia	73%	77%	63%	73%
Nausea	67%	75%	68%	70%
Anaemia	68%	64%	63%	66%
Fatigue	58%	61%	79%	63%
Decreased appetite	48%	52%	74%	54%
Weight decreased	50%	50%	42%	49%
Diarrhoea	37%	48%	47%	42%
Neutropenia	42%	41%	21%	38%
Vomiting	38%	43%	21%	37%
Hyponatraemia	30%	41%	37%	35%
Leukopenia	25%	41%	26%	31%

STORM Part 2 vs SVD (RP2D) Treatment Emergent Adverse Events (≥ 10% of STORM Patients)

Hematologic	STORM Part 2 (N=123) Selinexor 80mg + 20mg Dexamethasone Twice-Weekly	STOMP Study (N=26) 100 mg Selinexor (QW) + 1.3 mg/m^2 Borexomib (QW) RP2D
Thrombocytopenia	73%	39%
Nausea	70%	81%
Anemia	66%	35%
Fatigue	63%	69%
Decreased appetite	54%	62%
Weight loss	49%	19%
Neutropenia	38%	23%
Vomiting	37%	39%
Leukopenia	31%	4%
Lymphopenia	16%	-
Dysgeusia	10%	12%
Blurred vision	10%	23%

STORM Part 2: Overall Survival by Response



Number at Risk									
ORR Responders	32	31	27	22	13	10	8	4	2
Minimal Response	16	15	13	11	6	3	2		
Stable Disease	48	42	30	19	13	10	4	3	1
Progressive Disease	26	11	8	7	4	2			

STORM Part 2: Most Frequent SAEs

	Preferred Term	Selinexor + Dex[1] (N=123) Any SAE	Selinexor + Dex[1] (N=123) Any Treatment-related SAE
All		74 (60%)	34 (28%)
Hematologic	Thrombocytopenia	2%	2%
	Anemia	3%	<1%
Non-Hematologic	Pneumonia	11%	2%
	Sepsis	9%	2%
	Mental state changes	4%	0%
	Fatigue	3%	2%
	General physical health deterioration	3%	2%
	Acute kidney injury	2%	2%
	Dehydration	2%	2%
	Diarrhea	2%	2%
	Hyponatremia	2%	2%
	Confusional state	2%	1%
	Pyrexia	2%	0%

Selinexor Activity in Multiple Myeloma in Phase 1 Study KCP-330-001

	<70 mg (4 to 65)		~ 80 mg (70 to 90)		>90 mg (95 to 150)	
	Dex (n=13)	No Dex (n=27)	Dex (n=17)	No Dex (n=5)	Dex (n=16)	No Dex (n=3)
Best Response						
PR or better	0	0	7 (41%)	0	0	0
MR	3 (23%)	5 (19%)	2 (12%)	0	3 (19%)	0
SD	4 (31%)	12 (44%)	4 (24%)	1 (20%)	6 (38%)	2 (67%)
PD / NE	6 (46%)	10 (37%)	4 (24%)	4 (20%)	7 (44%)	1 (33%)

STORM Part 2: Overview of TEAEs Leading to Death

	Age/ Sex	AE Leading to Death	First Dose to Event Onset (days)	Last Dose to Event Onset (days)	Last Dose to Death (days)	Past Medical History
1.	65/M	Sepsis (non-neutropenic)	9	1	1	Coronary artery disease (CAD), hepatic vein thrombosis, leishmaniasis
2.	78/M	Pneumonia* (PD) (non-neutropenic)	26	9	9	Myocardial infarction, atrial fibrillation, hypercreatininemia, hyperglycemia
3.	75/M	Cardiac disorder	68	16	16	Hypertension, paraplegia
4.	62/F	Sepsis (fungal) (non-neutropenic)	46	8	17	Pneumonia, hypotension
5.	67/M	Sepsis* (non-neutropenic)	55	17	20	CAD, peripheral vascular disease
6.	68/F	Sepsis (PD) (non-neutropenic)	56	16	24	Thrombocytopenia, anemia
7.	55/M	Multi-organ dysfunction (PD)	38	23	24	Kidney disease, anemia, hypertension
8.	84/M	Respiratory arrest	61	25	25	Heart failure, atrial fibrillation, kidney disease, hypertension
9.	52/M	Pneumonia (RSV) (non-neutropenic)	14	3	27	Osteonecrosis of jaw, paraspinal mass
10.	59/M	Subdural hematoma (PD)	77	26	27	Atrial fibrillation, atrial flutter, thrombocytopenia

*Related to selinexor per treating physician PD = disease progression; RSV = respiratory syncytial virus